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Neural Tube Defects in North Carolina

N.C. Birth Defects Monitoring Program

1989-1993

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Neural Tube Defects in North Carolina:

Epidemiologic Characteristics and Trends among Live-Born and Still-Born Infants

State Center for Health Statistics
Department of Health and Human Services
Raleigh, North Carolina

State of North Carolina
James B. Hunt Jr., Governor

Department of Health and Human Services
H. David Bruton, M.D., Secretary

State Center for Health Statistics

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September 1997

700 copies of this public document were
printed at a cost of $228.76 or 33¢ per copy.

Printed on Recycled Paper

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SUMMARY

Neural tube defects (NTDs) are commonly occurring, serious birth defects that affect the brain and spinal column. These conditions, which include anencephaly, spina bifida, and encephalocele, may lead to infant death or severe physical and neurological disabilities. NTDs occur more often in North Carolina and in the other southeastern states than elsewhere in the U.S. In North Carolina about 80-100 affected infants are born each year.

A large proportion of neural tube defects can be prevented though daily consumption of the B-vitamin folic acid by the mother before pregnancy and during the first trimester. Because of their potential for prevention and because of the high rate of NTDs in North Carolina, efforts aimed at promoting use of folic acid are underway in many areas of the state. This report provides baseline information on the epidemiology of NTDs in North Carolina to facilitate the design and evaluation of effective interventions. Descriptive data on 430 infants with NTDs delivered between 1989 and 1993 are presented. Maternal risk factors for NTDs were evaluated using data for these 430 infants and a random sample of unaffected live births for controls.

The highest rates of NTDs were found to occur in the western and southeastern parts of the state. The rate in the western region was 56 percent higher than the overall state rate—a difference that is statistically significant. Maternal factors associated with an increased risk for NTDs include white race, low educational attainment, late entry into prenatal care, and obesity. There were some differences in the patterns of these risk factors among the three types of neural tube defects.

Earlier this year, the N.C. Birth Defects Monitoring Program implemented an active surveillance system for NTDs. This new surveillance system will provide more complete, accurate, and timely information on the occurrence of neural tube defects to support ongoing prevention and research activities in North Carolina.

BACKGROUND

Neural tube defects (NTDs), which include anencephaly, spina bifida, and encephalocele, are among the most commonly occurring preventable birth defects in North Carolina. Each year in the state, about 80-100 infants are born with NTDs, with perhaps an additional 50 affected pregnancies being terminated prior to birth (NCBDMP, 1996).

Neural tube defects are a group of embryologically related conditions which result from the failure of the neural tube to close during the third or fourth week of pregnancy. The neural tube is the embryonic structure that eventually forms the brain and spinal cord of the fetus. Anencephaly is a condition in which the cranial (head) end of the neural tube fails to close, resulting in the failure of the cranial vault and much of the brain to develop (Figure 1a). Infants with anencephaly are either stillborn or die shortly after birth. Spina bifida occurs when the middle or tail-end of the neural tube fails to close, leaving part of the spinal cord and its membranes exposed (Figure 1b). Infants with spina bifida experience muscle weakness or paralysis, loss of bladder and bowel control, and other complications. Encephalocele is a defect in the skull, usually in the occipital (back) region, through which a portion of the brain and its membranes protrude outside the cranium (Figure 1c). These infants often experience mental retardation or neurological deficits.

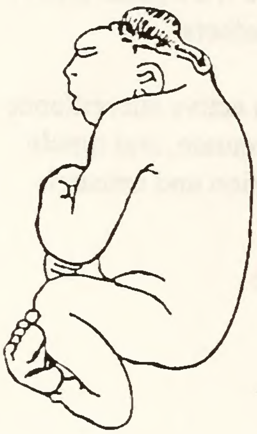


Figure 1a
Anencephaly

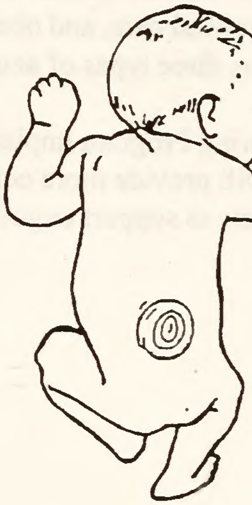


Figure 1b
Spina Bifida

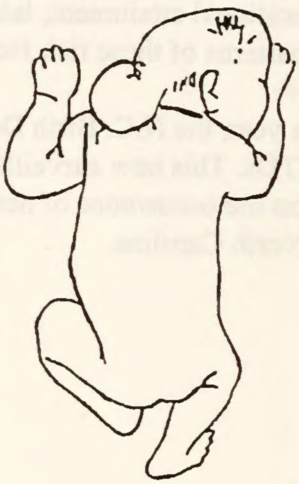


Figure 1c
Encephalocele

Because many infants with NTDs require special medical care throughout their lives, the economic costs of these conditions are considerable. The estimated lifetime costs for a child born with spina bifida is $294,000 (CDC, 1995). Based on this estimate, for North Carolina the total lifetime costs for infants born each year with spina bifida is nearly $15 million. In-patient hospital costs for children under age 18 with spina bifida in North Carolina exceed $3.5 million each year, $1.7 million of which was for children receiving Medicaid. Medicaid paid claims during the first year of life for infants with spina bifida in the state averaged over $850,000 each year.

Neural tube defects have a complex etiology which, despite considerable research, is not well understood. NTDs may result from single gene defects, chromosome abnormalities, maternal conditions such as diabetes, or certain teratogenic exposures such as valproic acid (an anticonvulsant drug) (Bjerkedal et al., 1982; Khoury et al., 1982; Robert and Guibaud, 1982; Becerra et al., 1990). In the majority of cases, however, the specific causes are unknown but are believed to arise from a combination of genetic and environmental factors (Elwood and Elwood, 1980; Khoury et al., 1982). Women who have had a previous NTD-affected pregnancy have a 2-3 percent recurrence risk; however, 95 percent of all NTD cases occur to women with no family history or other known risk factor (MRC, 1991).

There has been accumulating evidence that dietary factors—particularly deficiency of the B vitamin folic acid—may play a significant role in the occurrence of NTDs. Since the early 1980's, several studies have demonstrated that women who supplemented their diets daily with folic acid during the periconceptional period had a substantially reduced risk of giving birth to an infant with a neural tube defect (Smithells et al., 1983; Mulinare et al., 1988; Bower and Stanley, 1989; Milunsky et al., 1989; Vergel, 1990; MRC, 1991). In one of the largest randomized controlled studies, women who had had a previous NTD-affected pregnancy and who began taking 4 mg of folic acid per day prior to their next pregnancy had a 72 percent reduced risk of having a subsequently affected pregnancy (MRC, 1991).

As a result of these studies, the U.S. Public Health Service in 1992 issued a formal recommendation for preventing neural tube defects (CDC, 1992). The USPHS recommendation states: "All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg (400 micrograms) of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs" (CDC, 1992, p. 1). At this level of supplementation, an estimated 50-70 percent of all NTDs can be prevented. Sources of folic acid include multivitamins containing folic acid, fortified cereals, and other dietary sources of folate such as spinach and other leafy green vegetables, dried beans, and fresh citrus fruits. A 1996 ruling by the FDA requires that all products made with enriched flour or grain must be fortified with 140 micrograms of folic acid per 100 grams of grain, effective January, 1998. However, at this level of fortification it is estimated that only between 4-20 percent of folic acid-preventable NTDs can be averted. Therefore, CDC has continued to encourage women of childbearing age to increase folic acid intake through either dietary or multivitamin supplementation.

In North Carolina, efforts to promote folic acid intake are also underway. In 1995, the UNC Birth Defects Center, Duke University Medical Center, the March of Dimes, the Division of Maternal and Child Health, and other public and private agencies sponsored a one-day workshop aimed at developing strategies for increasing folic acid awareness. One outcome of this workshop was the creation of the Neural Tube Defect Prevention Task Force, which was charged with implementing the recommendations from the workshop participants. In 1996, the North Carolina chapters of the March of Dimes provided funding for the Birth Defects Monitoring Program to develop an enhanced NTD surveillance project. One of the major goals of this project is to provide data needed to develop effective programs aimed at promoting folic acid awareness and reducing the occurrence of NTDs in the state.

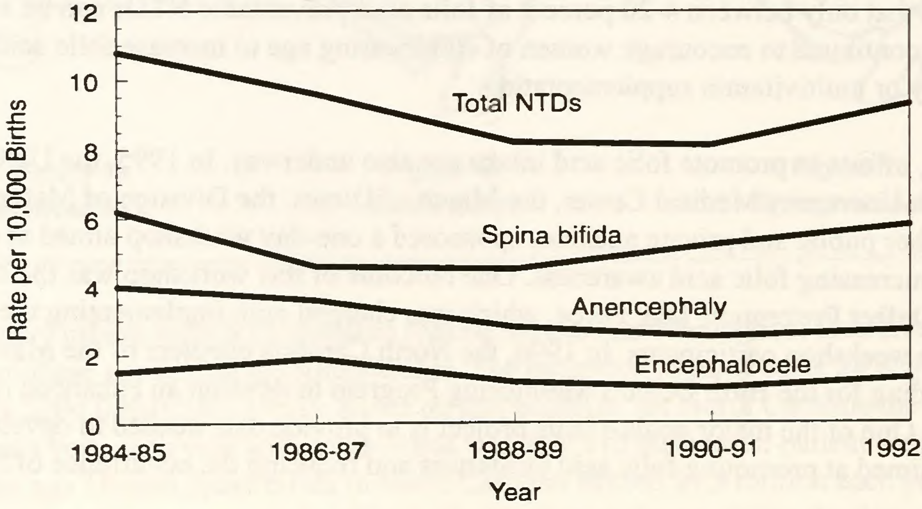
The intent of this report is to present an overview of the epidemiology of neural tube defects in North Carolina, and to provide baseline data for future surveillance and prevention initiatives. Unless otherwise indicated, all data presented in this report are for North Carolina resident live births and fetal deaths delivered between 1989 and 1993. It is important to note that the data in this report do not include NTDs that were prenatally diagnosed and terminated, or that resulted in fetal loss prior to 20 weeks gestation. Because as many as one-half of all clinically recognized NTDs may result in elective termination or early spontaneous abortion, the data presented in this report may not accurately reflect the actual geographic patterns and other epidemiologic characteristics of *all* neural tube defect cases diagnosed in the state.

EPIDEMIOLOGY OF NEURAL TUBE DEFECTS IN NORTH CAROLINA

Characteristics of Affected Infants

Between 1989 and 1993, there were 430 infants born with neural tube defects in the state, or about 80-100 infants per year. Of these, 129 infants (30 percent) had anencephaly, 253 (59 percent) had spina bifida without anencephaly, and 48 (11 percent) had encephalocele without other NTDs. The proportion of encephalocele relative to anencephaly and spina bifida is somewhat higher in North Carolina than in many other states, where encephalocele usually accounts for only about five percent of all NTDs. The rates for NTDs during the period 1989 through 1993 were 2.5 per 10,000 live births for anencephaly, 4.9 for spina bifida, and 1.2 for encephalocele (NCBDMP, 1996).

Figure 2. Rate of Neural Tube Defects Among Live-Born and Still-Born Infants, NC, 1984-1993



Among the 129 infants with anencephaly, only 47 percent were born alive, with the remainder being still-born. By comparison, among infants with spina bifida 94 percent were live births, while 85 percent of the infants with encephalocele were born alive. Excluding infants with anencephaly (which is invariably lethal), survival rates for live-born infants with NTDs are fairly high. Eighty-eight percent of infants with spina bifida survive their first year of life, while survival for infants born with encephalocele is somewhat lower (68 percent). There has been little change in these survival rates since 1984. Mortality among all infants with NTDs is highest during the neonatal period (birth to 28 days).

Overall, NTDs are more common among female than among male infants, with about 60 percent of all affected infants being female. The ratio of male to female cases (sex ratio) is 0.41 for anencephaly, 0.63 for encephalocele, and 0.77 for spina bifida.

NTDs often occur with defects involving parts of the body or organs other than the central nervous system, often as a part of a malformation syndrome or association. Sometimes, these anomalies arise as a result of the primary defect—for example, club foot in infants with spina bifida. Infants with anencephaly have the highest rate of multiple malformations (85 percent). About 60 percent of infants with spina bifida and encephalocele have defects in other organ systems.

Temporal Trends

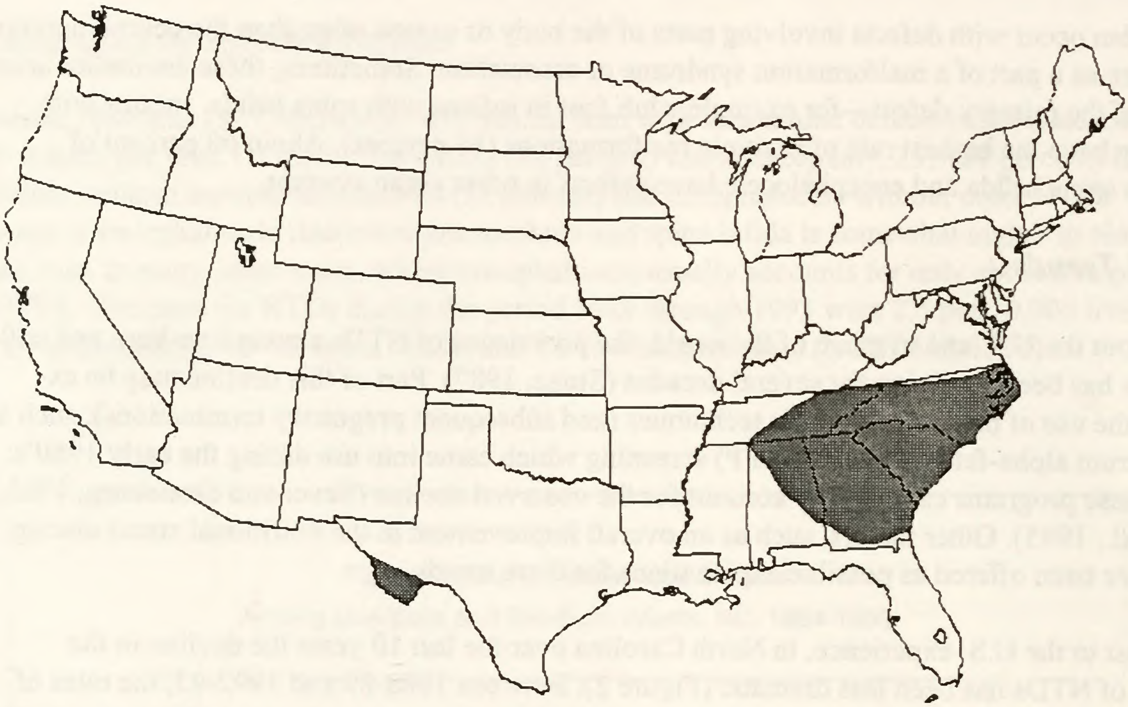
Throughout the U.S. and in much of the world, the prevalence of NTDs among live-born and still-born infants has been declining for several decades (Stone, 1987). Part of this decline may be explained by the use of prenatal diagnosis techniques (and subsequent pregnancy terminations), such as maternal serum alpha-fetoprotein (MSAFP) screening which came into use during the early 1980's; however, these programs cannot fully account for the observed decline (Sever and Strassburg, 1985; Roberts et al., 1995). Other factors, such as an overall improvement in the nutritional status among women, have been offered as possible explanations for these trends.

In contrast to the U.S. experience, in North Carolina over the last 10 years the decline in the prevalence of NTDs has been less dramatic (Figure 2). Between 1988-89 and 1992-93, the rates of anencephaly and encephalocele appear to have leveled off, while the rate of spina bifida has actually increased slightly. In 1993, the latest year for which we have data, the rate of spina bifida was 4.4 per 10,000 live births, the rate for anencephaly was 2.2, and the rate for encephalocele was 1.3. The overall rate for all NTDs in 1993 was 7.9 (NCBDMP, 1996).

Geographical Patterns

Much of the southeastern United States, including North Carolina, is considered to be a high-prevalence area for NTDs (Figure 3). In a recent study that compared spina bifida prevalence rates among 16 states with operational birth defects surveillance programs, North Carolina's rate was the third highest overall, and the highest rate among those states with passive reporting systems (CDC, 1996). The reason for the high rates in North Carolina and the other southeastern states is unclear.

Figure 3. High Prevalence Areas for Neural Tube Defects in the United States[1]



[1] Based on birth prevalence rates for open spina bifida among whites, 1973-1980. Shaded areas represent regions in which the rate is 8.0/10,000 or higher. From CDC, Am. J. Obstet. Gynecol. 145:570, 1983.

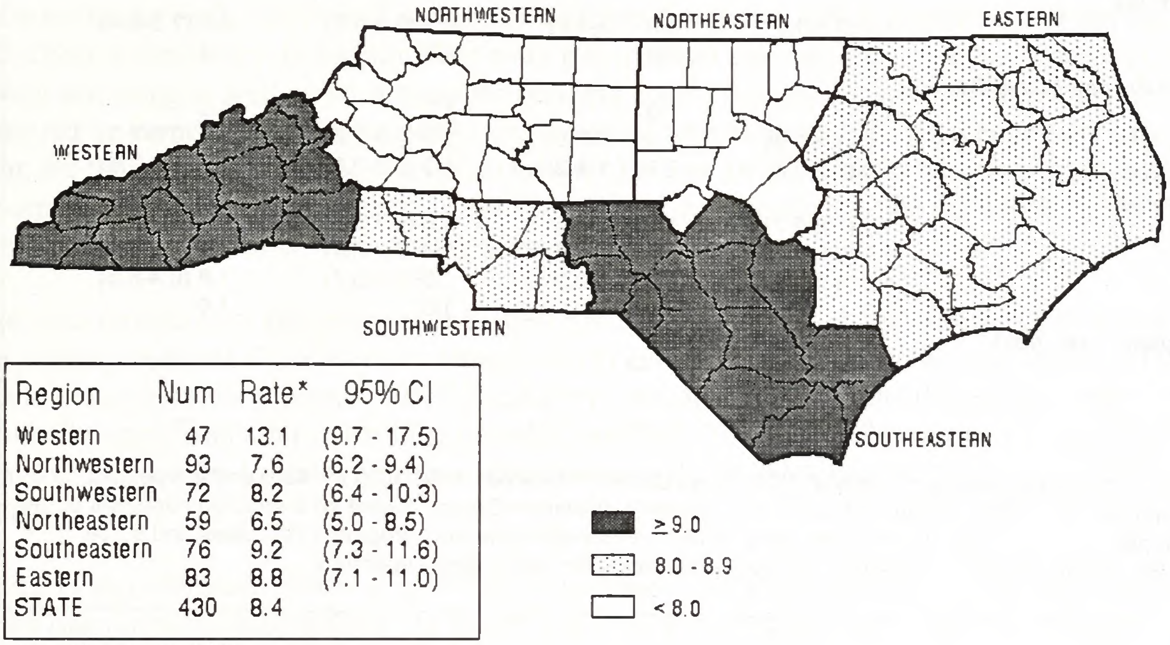
Evaluating the geographic patterns of NTDs within North Carolina at the county level is problematic due to the relatively small number of cases within individual counties. When aggregated into larger areas (e.g., perinatal care regions), some generalizations can be made (Figure 4). The highest rate of NTDs in the state is found in the western region, where the rate of 13.1 is significantly higher than that of the state overall. Further investigation of the increased rates in this region is underway. The rate in the southeastern region (9.2) is also higher than the state rate, but the difference is not statistically significant.

In the southwestern and eastern regions, the rates are similar to that of the state. The lowest rates are found across the Northern Piedmont area of the state–the northeastern and northwestern perinatal care regions—with rates of 6.5 and 7.6, respectively. It is important to note that, although low for North Carolina, the rates in these two regions are still high compared to that of many other areas of the U.S.

Maternal Sociodemographic Risk Factors

Table 1 presents adjusted odds ratios for selected maternal characteristics and the risk for NTDs for North Carolina residents. These data were derived from a case-control study that included all infants with NTDs who were born between 1989 and 1993 (cases), and a five percent random sample of all unaffected, live-born infants delivered during the same period (controls).

Figure 4. Total Neural Tube Defects by Perinatal Region, NC, 1989-1993



Region	Num	Rate*	95% CI
Western	47	13.1	(9.7 - 17.5)
Northwestern	93	7.6	(6.2 - 9.4)
Southwestern	72	8.2	(6.4 - 10.3)
Northeastern	59	6.5	(5.0 - 8.5)
Southeastern	76	9.2	(7.3 - 11.6)
Eastern	83	8.8	(7.1 - 11.0)
STATE	430	8.4	

*Per 10,000 Live Births

Table 1. Adjusted Odds Ratios and 95% Confidence Intervals for Selected Maternal Risk Factors and NTDs[1]

	All NTDs	*Anencephaly*	*Spina Bifida*	*Encephalocele*
	n=411	n=116	n=247	n=47
	AOR (95% CI)	*AOR (95% CI)*	*AOR (95% CI)*	*AOR (95% CI)*
Race				
White	1.5 (1.1-1.9)	1.2 (0.8-1.9)	1.4 (1.0-2.0)	2.9 (1.3-6.3)
Other[2]	1.0	1.0	1.0	1.0
Smoking				
Yes	0.8 (0.6-1.1)	0.6 (0.4-1.1)	0.8 (0.6-1.1)	1.5 (0.8-3.0)
No[2]	1.0	1.0	1.0	1.0
Parity				
0	1.1 (0.9-1.4)	0.7 (0.4-1.0)	1.3 (0.9-1.7)	1.7 (0.9-3.3)
1-3[2]	1.0	1.0	1.0	1.0
>3	1.4 (0.8-2.4)	0.9 (0.3-2.8)	1.7 (0.9-3.5)	1.1 (0.1-8.3)
Education				
Less Than High School	1.7 (1.2-2.4)	1.8 (1.0-3.2)	1.9 (1.3-2.9)	0.9 (0.4-2.3)
High School Graduate	1.4 (1.1-1.8)	1.5 (1.0-2.5)	1.5 (1.1-2.0)	0.9 (0.4-1.8)
Beyond High School[2]	1.0	1.0	1.0	1.0
Marital Status				
Single	1.0 (0.8-1.3)	0.9 (0.5-1.4)	0.9 (0.6-1.3)	3.1 (1.5-6.4)
Married[2]	1.0	1.0	1.0	1.0
Trimester Prenatal Care Began				
1st[2]	1.0	1.0	1.0	1.0
2nd	1.4 (1.1-1.8)	1.6 (1.0-2.5)	1.3 (0.9-1.8)	1.4 (0.6-2.9)
3rd/No Care	1.8 (1.2-2.6)	2.2 (1.1-4.2)	1.3 (0.8-2.3)	3.0 (1.2-7.6)
Mother's Age				
<20	1.5 (0.8-2.7)	1.5 (0.6-4.3)	1.6 (0.7-3.6)	1.0 (0.2-5.4)
20-29	1.5 (0.9-2.6)	1.2 (0.5-2.9)	1.8 (0.9-3.7)	1.2 (0.3-5.1)
30-34	1.6 (1.0-2.8)	1.3 (0.5-3.3)	1.8 (0.9-3.7)	1.8 (0.4-8.5)
>34[2]	1.0	1.0	1.0	1.0
Pre-Pregnancy Wt. (lbs)[3]				
<110	1.2 (0.7-2.0)	—	—	—
110-169[2]	1.0	—	—	—
>169	1.8 (1.2-2.6)	—	—	—

[1] Based on a logistic regression analysis all NTD cases delivered between 1989-1993 (n=430) and a 5 percent random sample of unaffected infants as controls (n=25,841). [2]Referent Group. [3]Based on a subgroup analysis of the above sample, which included women who were enrolled prenatally in the WIC program (129 cases and 8,784 controls). Sample size was insufficient to calculate odds ratios for each defect separately.

In most respects, the sociodemographic risk factors for NTDs in North Carolina are similar to those reported in the literature (see Little and Elwood, 1991; Elwood et al., 1992). The risk factors for the three major types of NTDs tend to differ, which suggests different etiologies for these defects.

Consistent with data from other states, in North Carolina the risk for NTDs tends to be somewhat higher among whites than among African American women. Controlling for other variables, the risk of all NTDs among whites is 1.5 times that of minority women. The risk is especially high for encephalocele, in which the rate for whites is almost three times that of minorities.

Smoking generally has not been found to be strongly associated with the risk for NTDs, and this pattern tends to hold for North Carolina as well. Among smokers, there was a slightly increased risk for encephalocele, and a slightly decreased risk for anencephaly; however, neither risk was statistically significant when controlling for other variables.

Some studies have shown that nulliparous women and mothers with high parity are more likely to have an infant affected with a neural tube defect. In North Carolina, nulliparous mothers had a slightly increased risk for encephalocele. Among women with parity of four or more, the risk for spina bifida was somewhat increased. Neither risk was statistically significant.

Low socioeconomic status has been linked to an increased risk for neural tube defects in several studies, an observation that is clearly apparent in North Carolina also. Compared to women with education beyond high school, women without a high school degree had an almost two-fold higher risk for anencephaly and spina bifida, while women with a high school diploma had about a 50 percent increased risk for these defects. Education was not associated with encephalocele. Single marital status, another measure of low socioeconomic status, is associated with a three-fold increased risk for encephalocele—but no increased risk for either anencephaly and spina bifida.

Women with delayed entry into prenatal care have a higher rate of NTDs. These women may have certain socioeconomic, nutritional, and lifestyle factors that place them at higher risk for having an NTD-affected pregnancy. In addition, late entry into prenatal care can limit a woman's access to prenatal screening as well as her options for deciding whether to carry an affected infant to term. Compared to women who enter prenatal care during the first trimester, women who initiate care during the third trimester or who receive no prenatal care are twice as likely to deliver an infant with anencephaly and three times as likely to deliver an infant with encephalocele. However, there is no increase in the rate of spina bifida among these women.

Previous reports have suggested an increased risk for NTDs among both younger women and older women; in North Carolina this pattern is not as evident. In North Carolina, the risk of NTDs tends to be lowest among women ages 35 and above, although none of the differences in risk were statistically significant after controlling for other variables. The lower rates among women ages 35 and above may be due to better nutrition, increased use of prenatal diagnostic services, or other factors.

Shaw et al. (1996) and Werler et al. (1996) both reported an association between maternal obesity and the risk for neural tube defects, the higher risk among overweight women presumably being related to improper nutrition. Population-based data on pre-pregnancy weight are not available in North Carolina. It is possible, however, to examine this issue for a subset of mothers who were enrolled prenatally in the WIC program because pre-pregnancy weight is collected at the time of the initial visit. Based on a subset of WIC participants, women whose pre-pregnancy weight was 170 pounds or more were 1.8 times as likely to have an infant with a neural tube defect, compared to women whose weight before pregnancy was between 110 and 169 pounds. Pre-pregnancy weight of less than 110 pounds was not associated with an increased risk for NTDs.

COMMENT

Up to 70 percent of all NTDs can be prevented through the use of folic acid, and a number of educational programs and prevention activities are already underway across the state. To support these programs, the need for timely and accurate population-based data on NTDs is critical.

The N.C. Birth Defects Monitoring Program has made NTD surveillance a major priority. With the assistance of funding from the March of Dimes, the program has recently implemented an enhanced NTD surveillance initiative statewide. This initiative includes: active surveillance of NTDs and selected other major malformations in the state's tertiary hospitals; and voluntary reporting by each of the state genetics centers of prenatally diagnosed cases. Future updates of this report will include data collected from these additional reporting sources.

We hope that the present report as well as future NTD surveillance updates will be of use to those involved in designing, implementing, and evaluating neural tube defect prevention programs in North Carolina. We welcome and invite your comments and questions about this report, and your ideas for subsequent analyses and updates. For questions or comments please contact Robert Meyer at (919) 715-4476 (robert_meyer@mail.ehnr.state.nc.us)

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Acknowledgments

The author wishes to thank the following individuals for their contributions to this report: Dr. Paul Buescher, Dr. Anita Farel, Dr. Ziya Gizlice, and Dr. Tom Sadler for their thoughtful comments and suggestions on the manuscript; Diane Enright for preparing the maps; Jean Stafford for typesetting the manuscript; and the North Carolina Chapters of the March of Dimes for their support for the N.C. Birth Defects Monitoring Program.

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